35, 36 and 38 as originally filed, which were canceled without prejudice and disclaimer in Applicants' Preliminary Amendment filed on July 13, 1998; new claim 126 is supported in the specification at pages 28-29; support for the amendments to claim 26 may be found at pages 28-29; and support for the amendment to claim 28 may be found at pages 27-28, particularly at page 27, lines 14-18. Accordingly, the present amendments do not add new matter, and their entry is respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 1-5, 8, 10, 12-16, 18, 20-23, 41, 43, 46, 51-57, 61-66, 68, 71, 76, 81-85, 87-90, 97-102, 108-110, 112, and 114-116 have been canceled as being drawn to non-elected restriction groups, new claims 117-126 are sought to be entered, and claims 26 and 28 have been amended. These amendments do not introduce new matter into the application. Upon entry of the foregoing amendments, claims 26, 28, 33, 34, 37, 39, 40, and 117-126 are pending in the application, with claim 26 being the sole independent claim.

III. Summary of the Office Action

In the Office Action, the Examiner made one objection to the specification and eight rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action.

IV. The Objection to the Abstract Is Accommodated

In the Office Action at page 2, section 1, the Examiner objected to the abstract of the disclosure because it exceeds 250 words. By the foregoing amendments, the abstract as filed has

been deleted, and the substitute abstract appended hereto is sought to be entered. As noted above, this amendment to the specification does not add new matter, as it consists solely of deletion of material from the abstract as originally filed so as to bring the abstract of the disclosure within the 250 word limit imposed by MPEP § 608.01(b). Hence, this objection has been fully accommodated.

V. The Obviousness-Type Double-Patenting Rejection

In the Office Action at pages 2-3, sections 2-4, the Examiner has provisionally rejected claims 26, 28, 33-34, 37 and 39-40 under the judicially created doctrine of obviousness-type double-patenting as being unpatentable over claims 158-159 of allowed co-pending U.S. Application No. 08/798,458 ("the '458 application"). Applicants respectfully disagree with the Examiner that claims 26, 28, 33-34, 37 and 39-40 are not patentably distinct from claims 158-159 of the '458 application. However, Applicants respectfully request that the Examiner hold this rejection in abeyance until identification of patentable subject matter in the present application, at which time Applicants will consider filing a terminal disclaimer.

VI. The Rejection Under 35 U.S.C. § 112, First Paragraph

In the Office Action at pages 3-5, sections 5-6, the Examiner rejected claim 28 under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> the specification, while being enabling for producing Avian Sarcoma Leukosis Virus Reverse Transcriptase (ASLV-RT) is not enable[d] for producing derivatives, variants fragments or mutants thereof. . . . the structural features required for other variants,

> derivatives, mutants and fragments of RT subunits are not discussed. For example, what is the required length for a fragment of RT or its subunits that can be functional alone or in combination with another subunit of RT? Further, on pages 27-28 the specification teaches more than one way by which the functional activities of such variants, mutants, derivatives and fragments may be identified. The specification fails to distinctly specify a single functional [criterion] by which such variants, derivatives, mutants etc. may be screened.

Office Action at page 2, section 6, lines 1-12. Applicants respectfully disagree with these contentions.

Claim 28 as currently presented recites derivatives, variants, fragments or mutants of the ASLV RT of claim 26 that have reverse transcriptase (RT) activity. Hence, to determine if a particular derivative, variant, fragment or mutant is encompassed within the scope of claim 28, one of ordinary skill would simply need to determine whether the derivative, variant, fragment or mutant has RT activity. As the Examiner has acknowledged, the present specification teaches a variety of assays (particularly at pages 27-28) to determine the functional activity of ASLV RTs, and derivatives, variants, fragments or mutants thereof. Thus, since the ASLV RT derivatives, variants, fragments and mutants of claim 28 are claimed in *functional* terms, the actual structure of these derivatives, variants, fragments and mutants is irrelevant. Moreover, since a variety of assays for determining the activity of such derivatives, variants, fragments and mutants of ASLV RT are taught in the present specification, one of ordinary skill could readily determine, without undue experimentation, whether or not a particular derivative, variant, fragment or mutant of ASLV RT would be encompassed within claim 28 as amended.

It is axiomatic that in order to enable a claimed invention, a specification need not teach, and preferably omits, information that is well-known to those of ordinary skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann*

Maschinenfabrik v. American Hoist and Derrick, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). In addition, one of ordinary skill in the art is deemed to know what is considered well-known. *See In re Howarth*, 210 USPQ 689, 692, (C.C.P.A. 1981). Applicants respectfully assert that screening assays for testing the activity of ASLV RT derivatives, variants, fragments and mutants were well-known in the art and were amply referenced and/or taught in the present specification as originally filed. Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use the ASLV RT derivatives, variants, fragments and mutants of claim 28 as amended, with a reasonable expectation of success and without undue experimentation.

In view of the foregoing remarks, Applicants respectfully assert that claim 28 as currently presented is fully enabled by the specification as originally filed. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are therefore respectfully requested.

VII. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Is Traversed

In the Office Action at page 5, sections 7-8, the Examiner has rejected claim 28 under 35 U.S.C. § 112, second paragraph, as being indefinite for depending from claim 26, which the Examiner contends is narrower in scope than is claim 28. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> [c]laim 28 is directed to a method of producing ASLV reverse transcriptase subunits as well as its variants, fragments, mutants,

> etc. This claim depends from claim 26 which is narrower in scope than claim 28.

Office Action at page 5, section 8, lines 3-5. Applicants respectfully disagree with these contentions. As one of ordinary skill would appreciate, the "derivatives, variants, fragments or mutants" recited in claim 28 are encompassed by the language of claim 26 which recites ASLV reverse transcriptase subunits without qualification (*i.e.*, without specifying whether or not these subunits are wild-type or full-length subunits). Hence, claim 26 as currently presented is sufficiently broad as to encompass the "derivatives, variants, fragments or mutants" recited in claim 28, which therefore does not broaden the scope of claim 26. Applicants therefore respectfully assert that claim 28 as currently presented particularly points out and distinctly claims the subject matter regarded by Applicants as the invention. Reconsideration and withdrawal of the rejection of claim 28 under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 102(b) Over Alexander Is Traversed

In the Office Action at pages 5-6, sections 9-10, the Examiner rejected claims 26, 28 and 33 under 35 U.S.C. § 102(b) as being anticipated by Alexander *et al.*, *J. Virol. 61*:534-542 (1987) (Doc. AT1, of record; hereinafter "Alexander"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> Alexander et al. teach the recombinant production of the alpha subunit of a Reverse Transcriptase from an Avian Sarcoma and Leukosis Virus (ASLV) using E. coli as a host (see the abstract) prior to this invention, anticipating claims 26 and 28. They also teach the isolation of the entire ASLV pol gene product (see page 539, Discussion section and figure 5) which involves coexpression of more than one subunit encoding region, anticipating claim 33.

Office Action at page 5, last line, to page 6, line 5. Applicants respectfully disagree with these contentions as they may be applied to the claims as currently presented.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Moreover, "[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996). Neither of these requirements is met by the disclosure of Alexander.

Claim 26 as amended (and hence the remaining claims that depend therefrom) is drawn to a method of producing an ASLV reverse transcriptase having a specific activity of from about 25,000 units per milligram to about 140,000 units per milligram. In contrast, the methods disclosed in Alexander do not produce ASLV RT having specific activities anywhere close to the activity of the ASLV RT of the invention as presently claimed. In fact, the specific activity of the enzymes produced in Alexander is never discussed in that reference, although Alexander does state that the majority of the ASLV RT produced was "located in insoluble inclusion bodies." *See* Alexander at page 537, col. 2, lines 10-12. In a subsequent publication from this same laboratory group (Soltis *et al.*, *Proc. Natl. Acad. Sci. USA 85*:3372-3376 (1988) (Doc. AS15, of record; hereinafter "Soltis")), it was demonstrated that ASLV RTs produced in *E. coli* by the methods disclosed in Alexander have extremely low specific activities; *see* Soltis at page 3374, Table 1, and at page 3376, col. 1, first full paragraph, lines 2-9. Thus, it is clear that Alexander does not disclose methods for the production of an ASLV RT having the specific

activity range as recited in claim 26 as amended (and the remaining claims that depend therefrom).

In view of the foregoing remarks, and under 35 U.S.C. § 102(b) in view of *Kalman* and *PPG Industries*, Applicants respectfully assert that Alexander cannot and does not anticipate the invention as presently claimed. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

IX. The Rejection Under 35 U.S.C. § 102(b) Over Soltis Is Traversed

In the Office Action at page 6, section 11, the Examiner rejected claims 26, 28, 34 and 40 under 35 U.S.C. § 102(b) as being anticipated by Soltis. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> Soltis et al. teach the recombinant preparation of the individual subunits of ASLV. They further prepare an AMV-RT heterodimer by mixing the individually isolated subunits (see their fig 5 and page 3375) prior to this invention anticipating claim 34.

Office Action at page 4, section 6, lines 2-5. Applicants respectfully disagree with these contentions.

As noted above, claim 26 as amended (and hence claims 28, 34 and 40 which depend therefrom) is drawn to a method of producing an ASLV reverse transcriptase having a specific activity of from about 25,000 units per milligram to about 140,000 units per milligram. As also noted above, the methods disclosed in Soltis do not produce ASLV RT having specific activities anywhere close to the activity of the ASLV RT of the invention as presently claimed. Instead, the ASLV RTs produced by the methods disclosed in Soltis have extremely low specific

activities; *see* Soltis at page 3374, Table 1, and at page 3376, col. 1, first full paragraph, lines 2-9. Thus, it is clear that Soltis does not disclose the presently claimed methods.

In view of the foregoing remarks, and under 35 U.S.C. § 102(b) in view of *Kalman* and *PPG Industries*, Applicants respectfully assert that Soltis cannot and does not anticipate the invention as presently claimed. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

X. The Rejection Under 35 U.S.C. § 102(b) Over Chernov Is Traversed

In the Office Action at page 6, section 12, the Examiner rejected claims 26, 37 and 39 under 35 U.S.C. § 102(b) as being anticipated by Chernov *et al.*, *Biomed. Sci.* 2:49-53 (1991) (Doc. AT3, of record; hereinafter "Chernov I"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> Chernov et al. (see abstract) teach the recombinant preparation [of] Rous sarcoma Virus (RSV) using E. coli, prior to this invention, anticipating claim 26. They also teach the modification of RNAse subunit of said enzyme with inhibitors of RNAse activity such as aziothymidine triphosphate (see fig 5), anticipating claims 37 and 39

Office Action at page 6, section 12, lines 2-6. Applicants respectfully disagree with these contentions.

As noted above, claim 26 as amended (and hence claims 37 and 39 which depend therefrom) is drawn to a method of producing an ASLV reverse transcriptase having a specific activity of from about 25,000 units per milligram to about 140,000 units per milligram. In contrast, Chernov I does not disclose the specific activity of the RSV RT produced by the methods disclosed therein. Moreover, in a prior publication from the same laboratory group (Chernov *et al.*, *Biokhimiya* 55:586-594 (1990); referred to herein as "Chernov II" and cited as

Doc. No. AR21 in Applicants' Fourth Supplemental Information Disclosure Statement (IDS) filed herewith, and an English-language abstract of which is cited as Doc. No. AS21 in the IDS), it was demonstrated that RSV RT produced by the methods disclosed in Chernov I have specific activities well below that of claim 37 as currently presented; *see* Chernov II at page 589, in Table 1, where the purified enzyme is shown to have a specific activity of 20.7 units/μg (*i.e.*, 20,700 units per milligram). Thus, Chernov I does not disclose a method for the production of an ASLV RT as recited in claim 37.

In view of the foregoing remarks, and under 35 U.S.C. § 102(b) in view of *Kalman* and *PPG Industries*, Applicants respectfully assert that Chernov cannot and does not anticipate the invention as presently claimed. Reconsideration and withdrawal of this rejection are therefore respectfully requested.

XI. The Rejection Under 35 U.S.C. § 103(a) Over Soltis and Müller Is Traversed

In the Office Action at page 7, section 15, the Examiner rejected claim 33 under 35 U.S.C. § 103(a) as being unpatentable over Soltis in view of Müller *et al.*, *J. Biol. Chem.* *264*:13975-13978 (1989) (Doc. AS12, of record; hereinafter "Müller"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> Soltis et al. teach the recombinant expression of alpha and beta subunits of ASLV. They also show that the alpha and beta subunits of ASLV-RT can be expressed in E. coli and that the properties of the soluble, enzymatically active proteins resemble those of the viral proteins. They further teach that alpha-beta heterodimer of ASLV-RT possesses several enzymatic activities, including an RNA dependent DNA polymerase, a DNA-dependent DNA polymerase, a DNA-RNA unwinding activity etc. which can be exploited in gene cloning. However, Soltis et al. do not teach obtaining high yields of the ASLV-RT protein by

> coexpression of the RT subunits in a single host. Muller et al. teach that heterodimer of HIV-1 Reverse Transcriptase in E. coli can be produced directly in high yields by coexpression of its subunits, simultaneously. It would have been obvious to one of ordinary skill in the art to use the individually cloned subunits of ASLV-RT of Soltis et al. and coexpress simultaneously in E. coli in order to obtain higher yields of ASLV-RT which has many useful activities for gene cloning.

Office Action at page 7, section 15, lines 3-14. Applicants respectfully disagree with these contentions.

As noted above, claim 26 as amended (and hence claim 33 which depends therefrom) is drawn to a method of producing an ASLV reverse transcriptase having a specific activity of from about 25,000 units per milligram to about 140,000 units per milligram. As also noted above, the methods disclosed in Soltis do not produce ASLV RT having specific activities anywhere close to those of the invention as presently claimed. Thus, Soltis does not disclose, suggest, or otherwise contemplate the presently claimed methods. In fact, Soltis actually teaches *away* from the presently claimed methods, by demonstrating that expression of ASLV RTs in *E. coli* primarily produces an insoluble, low-activity enzyme rather than the higher-activity ASLV RT of the present invention. Hence, Soltis is seriously deficient as a primary reference upon which to base an obviousness rejection.

The deficiencies in Soltis are not cured by the disclosure of Müller. As the Examiner has acknowledged, Müller is limited to a disclosure of methods for producing HIV RT by expressing the subunits of the HIV enzyme in *E. coli* host cells. The present claims, however, are drawn to methods for producing ASLV RTs rather than HIV RTs, and Müller does not disclose, suggest or contemplate the production of ASLV RTs by the methods described therein. Moreover, Müller does not cure the deficiencies of Soltis, particularly in the face of information in the art teaching away from the use of the methods described in Müller to produce ASLV RTs having

a specific activity of from about 25,000 units/mg to about 140,000 units/mg as presently claimed (*see, e.g.*, Alexander, Soltis, and Chernov I and II). Thus, Müller contains no guidance or suggestion that would supplement the insufficient disclosure of Soltis such that one of ordinary skill would have been motivated produce ASLV RTs by the presently claimed methods.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied since, as discussed above, there is no disclosure, suggestion, or contemplation in Soltis and Müller that would motivate one of ordinary skill to produce the presently claimed methods with any reasonable expectation of success. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See Fine*, 5 USPQ2d at1598.

Moreover, even assuming *arguendo* that the disclosures of Soltis and Müller could be properly combined, this combination would not enable one of ordinary skill to make and use the claimed methods. As noted above, attempts to produce ASLV RTs by methods analogous to those used to produce HIV RT in Müller result primarily in insoluble, low-activity enzyme (*see, e.g.*, Alexander, Soltis, and Chernov II). Indeed, as recently as 1999, those in the art did not use the *E. coli* production methods described in Müller to produce ASLV RT, since such methods did not produce ASLV RT of acceptable specific activity (*see* Werner *et al.*, *J. Biol. Chem.* *274*:26329-26336 (1999), cited as Doc. No. AR22 in the IDS filed herewith). Thus, at best, one of ordinary skill reading Soltis in view of Müller might have been motivated to try to produce ASLV RT using the *E. coli*-based methods for HIV RT disclosed in Müller. However, whether a particular combination of elements might be obvious to try is not a legitimate test of patentability, and therefore cannot support a rejection under 35 U.S.C. § 103. *See Amgen v. Chugai*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); *In re O'Farrell*, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988). In fact, since the disclosure of Soltis (and those of Alexander and Chernov I and II) actually teaches away from the presently claimed methods for the reasons noted above, one of ordinary skill probably would not have even been motivated to *try* to produce ASLV RT using the methods of Müller, and therefore would not have been motivated to combine the disclosures of Soltis and Müller.

Thus, the statutory burden required to sustain a *prima facie* case of obviousness has not been met. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Soltis and Müller therefore are respectfully requested.

XII. The Rejection Under 35 U.S.C. § 103(a) Over Alexander and Gerard Is Traversed

In the Office Action at page 8, section 16, the Examiner rejected claim 37 under 35 U.S.C. § 103(a) as being unpatentable over Alexander in view of Gerard *et al.*, *FOCUS 11*:66-69 (1989) (Doc. AR5, of record; hereinafter "Gerard"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that:

> Alexander et al. teach the recombinant production of the alpha subunit of ASLV using E. Coli as a host. Alexander et al. do not teach modification of the RNase H in order to reduce its activity during recombinant RT production. Gerard et al. teach that a major difficulty in cDNA synthesis is caused by RT RNase activity which results in low yields of cDNA synthesis. They further teach a strategy to improve the yield of Moloney Murine Leukemia Virus RT cDNA synthesis by deleting the portion of gene that codes for RNase H (see figure 4 for comparison of the effect of various deletions of RNAse H encoding gene on the yield of cDNA). It would have been obvious to one of ordinary skill in the art to use the expression method of Alexander et al. and fully or partially delete the RNase gene according to Gerard et al. in order to improve the yield of cDNA encoding the alpha subunit of ASLV-RT.

Office Action at page 8, section 16, lines 2-12. Applicants respectfully disagree with these contentions.

Applicants reiterate and incorporate by reference herein the remarks made above regarding the disclosure of Alexander as it might be applied to the present claims. Alexander does not disclose, suggest, or otherwise contemplate the presently claimed methods for producing an ASLV RT with the specific activity recited in claim 26 (and thus in claim 37 which depends therefrom). This deficiency in Alexander is not cured by the disclosure of Gerard. Hence, the statutory burden required to sustain a *prima facie* case of obviousness has not been met.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Alexander and Gerard therefore are respectfully requested.

XIII. Other Matters

A. The Status of the Claims

Applicants note that, at page 1 of the Office Action (Form PTO-326), the Examiner has indicated that claims 1-5, 8, 12, 16, 18, 20-23, 26, 28, 33-34, 37, 39-41, 43, 46, 51-57, 61-66, 68, 71, 76, 81-85, 87-90, 97-100 and 108-116 are pending in the present application. However, Applicants wish to remind the Examiner that, in the preliminary amendment filed in the present matter on July 13, 1998, Applicants canceled claims 6, 7, 9, 11, 17, 19, 24, 25, 27, 29-32, 35, 36, 38, 42, 44, 45, 47-50, 58-60, 67, 69, 70, 72-75, 77-80, 86, 91-96, 103-107, 111, and 113, without prejudice or disclaimer. Hence, Applicants respectfully assert that the correct listing of claims pending in the present application, prior to entry of the foregoing amendments, is claims 1-5, 8, 10, 12-16, 18, 20-23, 26, 28, 33-34, 37, 39-41, 43, 46, 51-57, 61-66, 68, 71, 76, 81-85, 87-90, 97-102, 108-110, 112 and 114-116. In any event, the pending claims in this listing, except for claims 26, 28, 33, 34, 37, 39 and 40, have been canceled by the foregoing amendments thus rendering this issue moot.

B. The Status of Claim 41

Applicants acknowledge the Examiner's statement at page 2 of the Office Action that claim 41 was inadvertently shown as grouped with Group V in the previous Office Action, when in fact it was not included in Group V in the Restriction Requirement (Paper No. 9). In any

event, claim 41 has been canceled without prejudice or disclaimer by the foregoing amendments solely as being drawn to a non-elected invention, rendering this issue moot.

XIV. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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